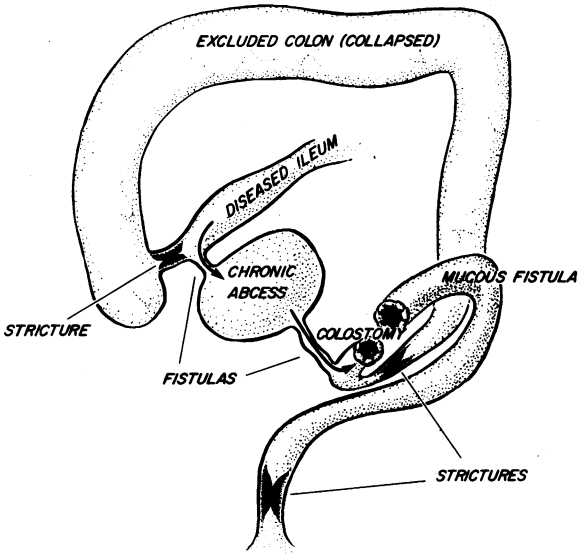

Figure 3.—The terminal ileum and colon were dramatically foreshortened and showed changes typical of chronic granulomatous enterocolitis. Structure (B) in Figure 2 was found to be a large chronic abscess cavity which filled by a fistula from diseased ileum and emptied via a fistula to the sigmoid loop which had been reversed during construction of the colostomy. Strictures explained the failure of the proximal colon to fill during radiographic examination.

tion and long-term rehabilitation. Malfunction of the stoma must be recognized, investigated and corrected if possible. A sigmoid colostomy should evacuate at regular intervals, once or twice a day; frequent discharge of liquid stool is clearly abnormal. Colostomy malfunction dating from the operation is usually due to inflammatory bowel disease, fistula, residual tumor or a serious technical flaw in the construction of the stoma. A patient who has profuse discharge from the stoma, difficulty with irrigation, or obstructive symptoms after initially good function should be examined for stenosis, prolapse, hernia, or recurrent disease.

The patient presented here was devastated both by her disease and its surgical management. Failure to recognize a problem and obtain an explanation caused severe distress over a protracted period.

Summary

A patient with Crohn's disease was incapacitated for five years by malfunction of a colostomy due to enterocavitary and sigmoidocavitary fistulas. She was rehabilitated by resection of diseased bowel and establishment of a permanent ileostomy.

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Cytomegalovirus Syndrome Post-Renal Transplantation

Treatment with Cytosine Arabinoside

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A CLINICAL SYNDROME occurring in four renal allograft recipients, consisting of prolonged fever, leukopenia and lymphocytosis which was attributed to cytomegalovirus (CMV) infection, was described in 1969 by Balakrishnan et al[1] and Andersen and Spencer.[2] The infection was documented by viremia and a rise in complement fixation (CF) antibody titer in the case reported by Balakrishnan et al and by viruria or a rise in the CF antibody titer in the three cases of Andersen and Spencer.[2] Remission occurred spontaneously in all four cases within one to two weeks of onset.

A similar clinical syndrome consisting of prolonged fever, leukopenia, lymphocytosis, hemolytic anemia and thrombocytopenia has been observed by us in nine childhood recipients of renal allografts.[3] Cytomegalovirus infection was documented by viremia, viruria or an increase in the CF antibody titer in each patient. This report describes the prompt remission of this clinical syndrome in a ten-year-old boy who had had an allograft, after treatment with cytosine arabinoside (Ara-C).

Report of a Case

The patient was a boy ten and a half years old who had been observed periodically at Children's Hospital of Los Angeles since age 15 months

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with a diagnosis of cystinosis confirmed by a slit lamp examination and bone marrow aspiration. Because of increasing symptoms of uremia, intermittent hemodialysis had been begun in April, 1971. He received a cadaveric allograft May 14, 1971. Tubular necrosis was severe and not until 19 days later was the allograft function sufficient to lower the blood urea nitrogen (BUN). A severe rejection episode occurred on day 21. It was resistant to increased immunosuppressive therapy and the allograft was removed on day 25. Intermittent hemodialysis was resumed and was continued until a second cadaveric renal transplant was carried out August 12, 1971. The allograft functioned immediately and postoperative dialysis was unnecessary. The clinical course of this patient after receiving the second allograft is shown in Chart 1.

On day 21 the patient began having daily temperature elevations to 40°C. The fever spikes occurred in the early morning and were accompanied by tachypnea, tachycardia and hypertension. Concomitant with the febrile episode were leukopenia (to a low of 1,400 per cu mm), rela-

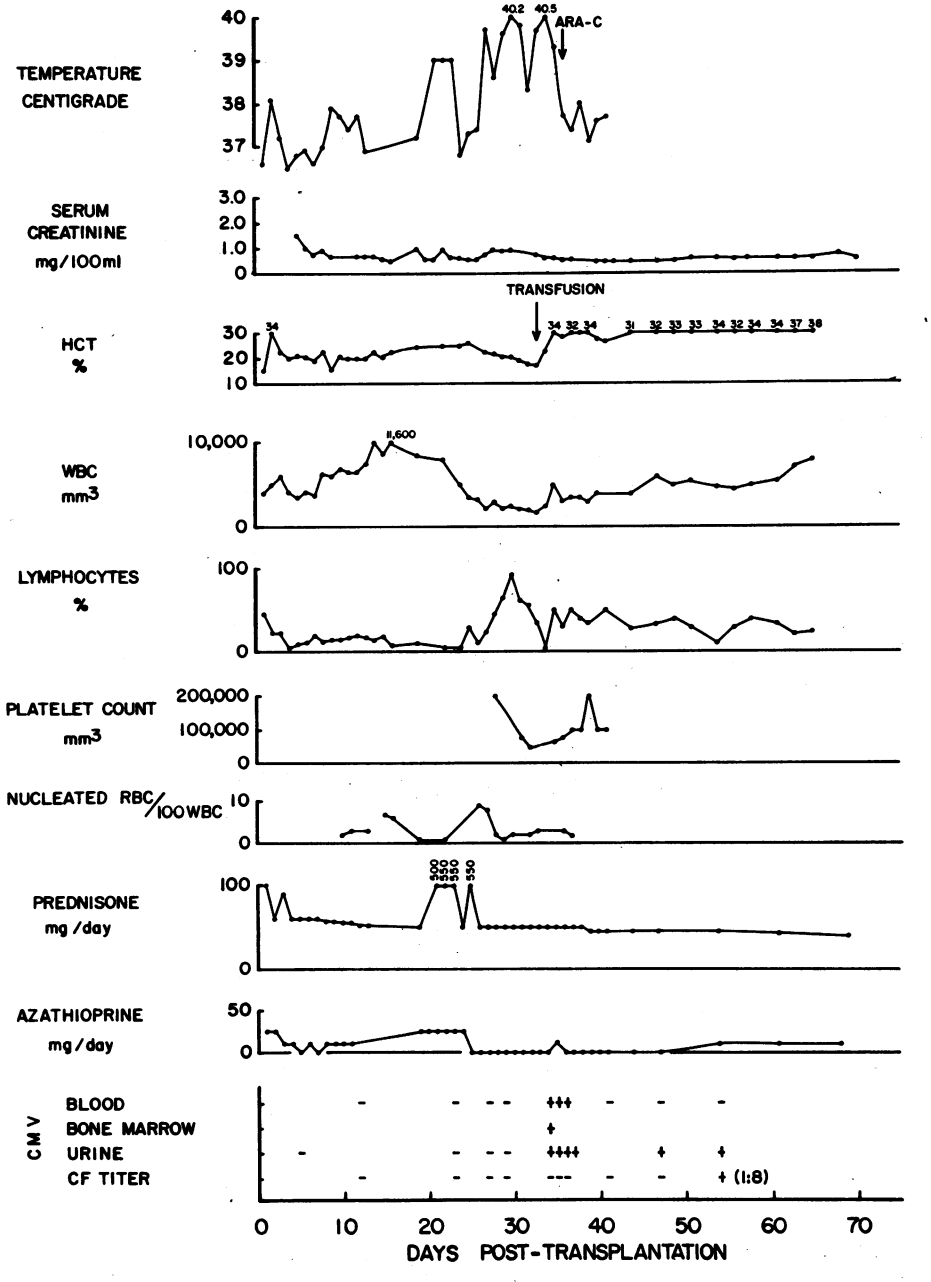

Chart 1.—Clinical course of patient in present case

tive lymphocytosis, thrombocytopenia (60,000 per cu mm), and anemia (the hemocrit fell to 18 percent before transfusion on day 33). Renal function as indicated by the serum creatinine level remained normal throughout the febrile period.

At first the fever was interpreted as a sign of rejection and the dosage of prednisone was increased (Chart 1). Azathioprine was discontinued on day 25 because of leukopenia and was not reinstituted until after remission of the febrile episode and elevation of the leukocyte count to more than 5,000 per cu mm on day 50.

The febrile period continued for 15 days and although the clinical and hematologic findings were consistent with CMV infection, neither cultural nor serologic confirmation was available during this period. The results of viral studies of the specimens submitted on day 34 became available only after clinical remission had occurred.

On day 35 it was decided that the persistence and severity of the clinical syndrome warranted a trial of Ara-C therapy. A rapid (5 minutes) intravenous infusion of 50 mg of Ara-C (3 mg per kg) was administered in the evening of day 35. On the following morning the characteristic early morning fever spike did not occur and two subsequent doses of Ara-C were given on days 36 and 37. The fever did not recur and the leukopenia, lymphocytosis and thrombocytopenia gradually remitted. No further clinical evidence of CMV infection has occurred and on the 82nd day after the allograft the serum creatinine was 0.6 mg per 100 ml.

Viral Studies

Collection of Specimens: A freshly-voided urine specimen (5 to 10 ml) or a specimen of blood (5 to 10 ml in a sterile, heparinized tube) were collected on the post-transplant days indicated in Chart 1. Bone marrow was collected on the 33rd post-transplant day. Ten milliliters of blood from each unit used for transfusion during the period of hemodialysis before the second transplant was collected and taken immediately to the Virus Research Laboratory for virus isolation and CF CMV antibody titer determinations.

Preparation of Specimens, Virus Isolation and Virus Identification: Specimens were prepared and viruses were isolated and identified as previously described.[4]

Serology: Plasma or serum was tested by a micro-complement-fixation test for antibody to human CMV antigen by the method of Sever et al.[5]

Results: Of six units of blood given to the patient before transplantation, two were found subsequently to have a CF titer of 1:8 or 1:16 for CMV. One of these units with a CF titer of 1:16 was administered 31 days before transplantation or 52 days before the onset of illness. This finding is suggestive evidence for the presence of latent CMV infection in blood donors, as previously reported.[6]

The results of the virus isolation studies from specimens of blood, urine and bone marrow before, during and after the febrile illness are shown in Chart 1. Cytomegalovirus was isolated from specimens of plasma buffy coat, urine and bone marrow on post-transplant day 34, 13 days after the onset of the clinical syndrome. Attempts failed to isolate CMV from specimens of plasma buffy coat or urine before or during the clinical illness on post-transplant days 5, 12, 23, 27 and 29. Although virus was isolated from the urine on three ooccasions after Ara-C was instituted (post-transplant days 37, 47 and 54), the virus was not isolated from the plasma buffy coat again. On post-transplant day 54 the patient's serum yielded a CF antibody titer of 1:8 for CMV.

Discussion

Histologic evidence of CMV infection has been frequently reported in postmortem examinations of renal allograft recipients.[2,7,8] The finding was usually fortuitous and not associated with clinical symptoms. Similarly, serologic evidence of CMV infection or cytomegaloviruria or both has been reported to occur frequently (22 percent to 73 percent)[2,4,8-10] in asymptomatic allograft recipients. The only reported clinical manifestations of CMV infection after renal transplantation have been the syndrome of prolonged fever and hematologic abnormalities[1,2] and the association of CMV with the transplant lung syndrome.[4,11]

The paucity of previous reports associating CMV infection with clinical manifestations in allograft recipients may be related to lack of persistent investigation. As shown in the present case, confirmation of CMV infections was not obtained until late in the clinical course. Previous descriptions have also indicated that the diagnosis of CMV infection usually is not made until after spontaneous remission of clinical symptoms.[1-3]

Although the causal role of CMV in the clinical manifestations of the present case cannot be unequivocally established, the association of CMV infection with the postperfusion syndrome[12] and heterophile-negative infectious mononucleosis,[13]

two entities that are manifested by prolonged fever and hematologic abnormalities, makes such a diagnosis likely.

Spontaneous remission usually occurs without significant morbidity in the above clinical syndromes ascribed to CMV; however, our experience has indicated the presence of significant morbidity in renal allograft recipients when the fever is prolonged—more than ten days—and when CMV infection is associated with transplant lung. Therefore, we decided upon a therapeutic trial of Ara-C when no spontaneous remission was evident after 15 days of illness.

Cytosine arabinoside is a pyrimidine nucleoside which inhibits deoxyribonucleic acid synthesis and has been shown to have potent antiviral activity *in vitro* against the human cytomegalovirus.[14] Recently, Ara-C has been used clinically to treat herpesvirus infections (varicella, zoster and simplex) both in previously healthy patients and in those with malignant disease. Dramatic clinical responses have been reported.[15] The response was usually rapid—within 24-72 hours—and the toxic side-effects were minimal. Because of these facts, Ara-C was selected for use in the present patient.

The response to Ara-C administration was dramatic. The fever spikes which had occurred daily for 15 days remitted immediately after the initial dose and did not recur. Likewise the hematologic abnormalities reverted to normal shortly after the initiation of Ara-C therapy.

Since the clinical syndrome which occurred in this patient has been observed to remit spontaneously in other patients, one may only speculate regarding the unequivocal therapeutic effect of Ara-C. However, the immediate response as manifested by the cessation of the febrile course seems significant.

The immediate response of the febrile course to Ara-C is possibly related to cessation of the viremia which could have been producing the fever. After the initiation of Ara-C therapy, CMV was no longer present in plasma buffy coat specimens. Conversely, cytomegalovirurla persisted for 16 days after Ara-C therapy. This may indicate that Ara-C is effective in eradicating viremia but possibly not in eliminating CMV from the kidney. Further trials in the use of Ara-C will be necessary to elucidate this point.

Summary

A ten-year-old boy recipient of a renal allograft acquired the cytomegalovirus syndrome, confirmed by virus isolations from his plasma buffy coat, urine and bone marrow, and a rise in the titer of cytomegalovirus complement-fixing antibody. Treatment with cytosine arabinoside after 15 days of clinical illness was followed by immediate cessation of the febrile course.

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